REMARKS

Amendments

The above amendment to the claims is supported in the specification at paragraph 0146, inter alia. This amendment is introduced to remove the overlap in subject matter with US 6,083,953, obviating the need for a terminal disclaimer. Thus, no new matter is introduced.

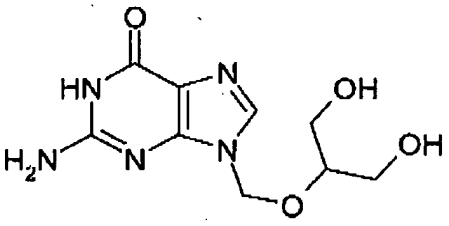
Claim 29 is canceled as redundant in view of the amendment of claim 23.

Rejection over Verheyden and Beauchamp

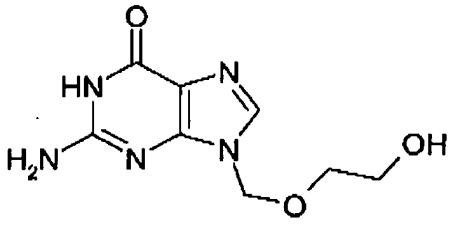
Claims 23-29 were rejected as obvious under §103(a) over Verheyden, US 4,355,032 in view of L.M. Beauchamp et al., Antiviral Chem Chemother (1992) 3(3):157-64 ("Beauchamp '92"). Applicants respectfully traverse.

Verheyden disclosed the preparation of ganciclovir and the sodium salt of ganciclovir, but did not disclose or suggest the preparation of ganciclovir esters. Beauchamp '92 disclosed the preparation of esters of acyclovir as prodrugs for acyclovir. Beauchamp '92 described problems with previous attempts at acyclovir prodrugs, in which (theoretically) the prodrug was phosphorylated prior to its conversion to the active drug, resulting in toxicity. "Therefore, we initiated a programme to develop an effective prodrug **that could not be phosphorylated prior to conversion** to acyclovir." (Beauchamp '92 at p. 157, col. 2; emphasis added.)

Ganciclovir differs from acyclovir in that, as the Examiner has noted, ganciclovir possesses an additional hydroxymethyl group[1]:



Ganciclovir



Acyclovir

[1] The additional hydroxymethyl group also introduces a chiral center if only one OH is esterified.

The question of whether to make a mono-ester or diester of acyclovir does not arise: acyclovir has only one hydroxy group to esterify. However, in the case of ganciclovir, esterifying only one of the two free hydroxy groups would leave one group available for premature phosphorylation. Thus, one of ordinary skill in the art would find that Beauchamp suggests that **both** ganciclovir OH groups should be esterified. In light of Beauchamp's stated motivation, one would find that Beauchamp's teaching is that **all** free hydroxy groups should be esterified or blocked in order to prevent premature phosphorylation. It just happens that acyclovir has only one hydroxy group to worry about.

Ganciclovir, however, has two available hydroxy groups. If one of ordinary skill in the art were to combine the teachings of Verheyden with those of Beauchamp '92, one would be lead inexorably to the ganciclovir **diester**, not the monoester. The diester is also active: as set forth in the Declaration of Susan Malcolm (previously submitted), ganciclovir bis-valinate HCl exhibits a bioavailability of 34.0% (± 2.37), a five-fold improvement over the bioavailability of the parent ganciclovir, 6.9% (± 0.76). However, surprisingly, the ganciclovir mono-valinate HCl exhibits a bioavailability of 55.4% (± 4.41), an improvement which is a factor of 1.6× better than the diester, and a factor of 8× better than the parent compound. The degree of improvement for ganciclovir is surprising because the improvement for acyclovir is only a factor of 3.8× (acyclovir = 14.2% ± 0.53; valacyclovir = 53.4% ± 9.40). Nothing in Verheyden or Beauchamp '92 would lead one to expect that the monoester would be desirable at all, much less that it would exhibit far superior properties. Unexpected results such as this, while not required, are strongly indicative of non-obviousness.

The Examiner has asserted that ganciclovir and acyclovir are "analogous" based on their structural similarity. The differences in their properties, due to that extra hydroxymethyl group, however are substantial. Again referring to the Declaration of Susan Malcolm, note that the bioavailability of acyclovir is reduced by a factor of two when one adds the extra hydroxymethyl group to obtain ganciclovir (14.2% for acyclovir vs. 6.9% for ganciclovir). Comparing the mono-esters, however, we see that adding the hydroxymethyl group to the acyclovir monoester **improves** the bioavailability (53.4% for valacyclovir vs. 55.4% for valganciclovir). This also is an unexpected and surprising result, and is evidence of non-obviousness.

Applicants respectfully submit that the rejection is thus overcome, and solicit the withdrawal of same.

Rejection over Beauchamp

Claims 23-29 were rejected as obvious under §103(a) over Beauchamp, US 5,043,399. Applicants respectfully traverse.

Beauchamp '399 disclosed amino acid esters of certain nucleoside analogs, and a limited number of salts thereof. Regardless of the number of possible compounds generically (or subgenerically) disclosed,[2] it is not disputed that the presently-claimed monoester is not disclosed specifically therein.

We assume that the inventor of Beauchamp '399 is the same Lilia M. Beauchamp of the above-cited reference, L.M. Beauchamp '92. As set forth in the section above, Beauchamp set forth her rationale for preparing antiviral prodrugs in Beauchamp '92: "to develop an effective prodrug that could not be phosphorylated prior to conversion to acyclovir." (Beauchamp '92 at p. 157, col.

[2] There are a variety of possible calculations for arriving at a genus of compounds. However, to constitute a valid comparison for evaluation as prior art, Applicants submit that the genus or subgenus must be as stated in the reference, not constructed ad hoc after the fact. Otherwise, we are selecting certain portions of the disclosure and discarding other portions, using the claimed invention as a guide. If one must be guided by Applicants' specification, then the reference is not truly evidence of obviousness at the time the invention was made (i.e., prior to filing Applicants' application). Thus, for example, Applicants agree that one may consider the preferred group of compounds as including only esters of cytosine and ganciclovir (col. 2, lines 13-14). As to the selection of esters, Beauchamp states that one uses "preferably neutral amino acids i.e. amino acids with one amino group and one carboxyl group. Examples of preferred amino acids include aliphatic acids, e.g., containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. ... the L-amino acids being most preferred." (col. 2, lines 19-29) This group would also include at least leucine and proline, making the group of amino acids at least 6. Further, the aliphatic acids are only "examples of preferred", not the only preferred amino acids: thus, neutral amino acids is the true "preferred" group. Note also that the claims are limited only to "naturally occurring neutral amino acid acyl residue", and that none of the claims are further limited to aliphatic amino acids. This group further includes methionine, phenylalanine, serine, threonine, cysteine, and tyrosine, making a total amino acid group of 12. Regarding the appropriate acids, there are of course more than the nine listed at col. 2, lines 34-36, e.g., propionic, butyric, benzoic, etc., that one might include. Beauchamp does not present this list as exhaustive, but only as an example of several appropriate acids. See, e.g., Applicants' specification at paragraph 0066, listing 46 exemplary acids.
Thus, the number of monoesters is either 12 (2 bases × 6 aliphatic acids) or 24 (2 bases × 12 neutral amino acids), with an equal number of symmetrical diesters. Nothing in Beauchamp suggests that both acids must be the same, and in fact the specification states that R and R^1 are **independently** selected: if the Examiner's assertion that Beauchamp enables the preparation of monoesters is correct, then obviously Beauchamp could have prepared a monoester with one acid, and further esterified it with a second, different acid to produce a mixed ester. Thus, the number of mixed esters with 2 bases is either 40 (assuming 6 aliphatic amino acids) or 154 (assuming 12 neutral amino acids). The total number of mono- and diesters is either 64 (12 + 12 + 40, using 6 aliphatic amino acids) or 202 (24 + 24 + 154, assuming 12 neutral amino acids). The resulting number of salts is at least 576 or 1818, assuming only 9 appropriate acid addition salts: consideration of all appropriate salts falling within Beauchamp's definition of "an appropriate acid" would increase these

2.) As set forth above, acyclovir differs from ganciclovir in that acyclovir has only one OH that can be phosphorylated (or esterified), while ganciclovir has two identical OH groups that can be phosphorylated (or esterified). What should one do with the extra CH_2OH group? Although Beauchamp '399 does not rule out the possibility of esterifying only one OH group, the later (presumably older and wiser) Beauchamp '92 clearly suggests that one should not leave a free OH group available for premature phosphorylation. Although the rationale is presented with traditional scientific understatement,[3] it must be remembered that this rationale was apparently sufficient to justify the preparation and animal testing of dozens of compounds as reported in Beauchamp '92 – a substantial corporate investment. Toxicity was observed, and Beauchamp's subsequent research was designed to overcome it. Applicants thus submit that Beauchamp '399 fails to render the instantly-claimed invention obvious.

Even if one were to consider the claimed ganciclovir mono-valine ester "obvious to try" in view of Beauchamp '399, or even if one finds that a prima facie case of obviousness is established, this is **rebutted** by the unexpected and surprising results exhibited by the claimed compound. As set forth above and in the Declaration of Susan Malcolm, valinating all of the available OH groups in acyclovir improves its bioavailability by a factor of 3.8×. Valinating all of the available OH groups in ganciclovir improves its bioavailability by a similar amount, a factor of 5×. However, valinating only half of the available OH groups (contrary to the teachings of Beauchamp '92) improves the bioavailability of ganciclovir by a factor of 8×. This is unexpected, surprising, and directly relevant to the utility of the compound.

Applicants respectfully submit that the rejection is thus overcome.

Amendment to the Specification

Applicant's preliminary amendment was objected to as introducing new matter through incorporation by reference of all parent applications. In presenting the amendment above, Applicants assume that the previously-presented amendment to the specification was not entered. Thus, the indicated changes are based on the specification prior to the amendment to which

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numbers by at least a factor of 4 or 5. Using only the 46 acids Applicants have listed (and this list is also non-exhaustive) results in 2944 or 9292 different compounds.

[3] "The toxicity of the two congeners, encountered in laboratory animals, was hypothesized to be the result of phosphorylation of the unconverted prodrug." (Beauchamp '92 at p. 157, col. 2.) By "hypothesized", Applicants assume Beauchamp meant that she had evidence that was convincing, but short of scientific certainty.

objection was made. If the preliminary amendment was in fact entered, please note that the last sentence of the preliminary amendment of this paragraph has been deleted.

Applicants submit that the above replacement avoids any introduction of new matter, and that the objection is thus overcome.

Double Patenting

Claims 23-29 were rejected for obviousness-type double patenting over claims 1-6 of US 6,083,953. Applicants submit that the rejection is overcome by the amendment above, which removes the overlap between '953 and the present application.

Conclusion

Applicants respectfully submit that all rejections are thus overcome, and that the application is now in condition for allowance. Such action is solicited.

Respectfully submitted,

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